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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
09/11/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/580,511	FUCHS ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 6/9/09, have been entered. Claims 6, 17-20 are cancelled; claims 1-5, 7-16 are pending and under current examination.

This action is non-final.

Election/Restrictions

Applicant's election of Group I (claims 1-16) in the reply filed on 12/1/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-5, 7-16 are under current examination.

Claim Objections

The prior objection of Claim 7 is withdrawn in view of Applicants' amendment to the claim which now recites "reporter protein".

Claim Rejections - 35 USC § 102

The rejection of claim 6 under 35 U.S.C. 102(b) as being anticipated by US Pat. No. 5,861,315 (Filed October 16, 1996; Issued January 19, 1999) is rendered moot in view of Applicants' cancellation of the claim.

The rejection of claims 9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat. No. 5,639,618 (Filed, May 13, 1994; Issued June 17, 1997, Applicants' IDS) is withdrawn in view of Applicants' arguments, regarding specific nucleic acids found in the cells.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,665,557 (Filed November, 1994; Issued September 9, 1997). The Examiner notes that this rejection contained a typographical error in the Patent Number. The correct Patent Number is now listed.

The claims are directed to a method for isolating a self-renewing, multipotent, slow-cycling cell comprising obtaining a population of cells from a sample and sorting the population of cells based on the presence of CD34 and the amount of a selected slow-cycling cell marker expressed by each cell. Further embodiments recite that the cell will differentiate into an epidermal, neuronal or glial cell.

The specification states that stem cells are slow-cycling, undifferentiated or immature cells that give rise to specialized cell types and ultimately to differentiated cells (p. 1, lines 12-15). Particularly, the specification defines that term "slow-cycling cell" as intending, "to include a stem cell (such as a pluripotent, multipotent, bipotential, and monopotent cell) which is an unspecialized cell that is capable of replication and self-renewal and can develop into specialized cells of a variety of cell types or lineages (p. 8, lines 24-30). The term "slow-cycling cell marker" is interpreted to mean any marker that is expressed in a slow-cycling cell. Given these definitions in the specification, the claims encompass isolating any type of stem cell utilizing the presence of CD34 and another marker that is expressed by said stem cell.

Regarding the limitations in claim 1, the '557 patent teaches methods of obtaining an enriched population of hematopoietic stem cells by obtaining a

population of human hematopoietic cells, separation of hematopoietic cells from a source, separating a subpopulation of cells utilizing a CDw109 antibody (see claim 1), and then using an additional maker to separate the cells, such as CD34, Thy-1 and rho (see claims 2-3).

Regarding the limitation in claims 2-5, the claims are product-by-process claims. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In the instant case, the '557 patent teaches hematopoietic stem cells, which fulfill the definition of a self-renewing, multipotent, slow-cycling.

Regarding the limitations of claims 3-5, these claims recite properties of the cell. These properties would be inherent to the stem cell. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are

necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7 and 9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. No. 5,639,618 (Filed May 13, 1994, Issued June 17, 1997, IDS) when taken with Strathdee *et al.* (Gene, 229: 21-29, 1999), Bohl *et al.*(Nat. Med., 3(3): 229-305, 1997) when taken with Mahmud *et al.* (Blood, 97(10): 3061-3068, 2001) and US Pat. No. 6,485,971 (filed September 18, 2000, Issued November 26, 2002).

Applicants' Arguments. Applicants traverse the rejection and argue that the Examiner has relied upon Mahmud and the '971 to teach the method steps as set forth in steps d)-g) of the instant claim 7. Applicants argue that there is simply no teaching or suggestion in any of the cited references of the combination of elements set forth in steps d)-g) of the instant claim 7. Mahmud, Applicants argue, teach the incorporation of BrdU into pluripotent HSCs to analyze the replicative history of the same, and the '971 patent appears to teach separation of cells based upon the level of transferring receptor, EGFR, IGFR and keratinocyte growth factor receptor expressed by a cell, and this does not constitute sufficient guidance for the steps of d) –g) of the instant claims. See page 8 of the Response. Applicants argue that a mere conclusory statement that steps d)-g) of the instant invention would have been obvious is not sufficient to establish a *prima facie* case of obviousness (see p. 9 of the Response).

Response to Arguments. These arguments have been considered, but are not persuasive. It is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

In the instant case, the Examiner contends that the combination of art as a whole is sufficient to arrive at the claimed invention. The '618 document, Strathdee and Bohl teach guidance for utilizing the nucleic acid sequences found in parts a)-c) of claim 7. With regard to parts d)-g) of claim 7, Mahmud *et al.* provide specific

guidance to show that multipotent stem cells, such as hematopoietic stem cells, are considered slow-cycling cells (see Abstract). Therefore, one of skill in the art would recognize that stem cells are slow-cycling cells. Additionally, enriching steps, such as those taught in the '971 document are also known in the art (col. 3, lines 49+-col. 4, lines 1-12, for example). Thus, Mahmud teach that pluripotent cells are slow-cycling, which would clearly maintain higher levels of reporter protein than cells that are dividing, and the '971 document provides clear guidance as to how to separate cells that have higher versus lower levels of protein expression. One of skill in the art would be further motivated, in view of the teachings of Mahmud and the '971 document, to inactivate the regulatable transcription factor (by, for example, the withdrawal of doxycycline in the case of using the Tet system), and select for slow-cycling stem cells by allowing the cells to divide, and selecting cells that contain a higher level of reporter protein expression. One of ordinary skill in the art would have been sufficiently motivated to make this modification in order to produce substantially pure populations of stem cells.

Rejection

The "618 document teaches methods of isolating a lineage-specific stem cell *in vitro* by transfecting an lineage specific stem cell with a construct comprising a regulatory region of a lineage specific gene operably linked to a DNA encoding a reporter gene and separating the cells which express the reporter protein from other cells in the culture (see Abstract). The '618 document teaches that enhancer specificity will direct expression of the surface protein at the desired stage of isolation and FACS will allow the efficient isolation of the desired stem cell (col. 4, lines 15-22). Thus, as a whole, the '618 document provides guidance for specifically isolating stem cells utilizing a promoter that is active in stem cells and using known cell sorting techniques.

However, the '618 document does not specifically teach that the nucleic acid sequence(s) that introduced into the stem cell encode a regulatable transcription factor operably linked to the stem cell specific promoter (claim 7, part a), and a nucleic acid sequence encoding a nucleic acid sequence encoding a reporter protein operably linked to a regulated promoter to which the regulatable transcription factor binds (claim 7, part b) such that upon expression of the stem cell specific promoter, the regulatable transcription factor increases expression of the reporter protein (claim 7, part c). However, prior to the time of filing, Strathdee teaches using the tetracycline-responsive system to provide efficient, tightly regulated, inducible gene expression system, using a bi-directional expression vector wherein the TK promoter is used to direct expression of the rtTA or tTA transactivator and the CMV element is used to direct cDNA expression. In particular, gene expression can be efficiently switched on and off using doxycycline and a selectable marker can be incorporated into the vector (see Abstract). Strathdee suggest that their system can be used to confine gene expression in a defined cell type (p. 29, second to last sentence). Additionally Bohl teach using tetracycline regulation of gene expression for muscle-specific expression of mouse erythropoietin (Epo) cDNA using a two vector system and found that gene expression increased 200 fold in response to myogenic cell differentiation and doxycycline stimulation (Abstract). Bohl teach that these vectors efficiently allow for cotransduction of primary cells and that the control of rtTA expression from a skeletal muscle specific promoter prevents the accumulation of the potentially toxic protein in vector-producing cells, and that the resultant cells stably expressed the vector over time (p. 303, 1st col., Efficient cotransduction of primary cells).

Neither the '618 document, Strathdee or Bohl specifically teach inactivating the regulatable transcription factor so that expression of the reporter protein is decreased, incubation of the cell for a sufficient amount of time so that the cell goes through one or more cell cycles to generate a population of cells, detecting the

amount of reporter in the population and then sorting the population of cells by the amount of reporter protein present in each cell, wherein sorted cells containing increased levels of the reporter is indicative of self-renewing, multipotent, slow-cycling cells. However, prior to the time of filing, Mahmud *et al.* provide specific guidance to show that multipotent stem cells, such as hematopoietic stem cells, are considered slow-cycling cells (see Abstract). Additionally, the concept of separating rapidly dividing cells from slow-cycling cells is known in the art. For example, the '971 document discusses enrichment methods for keratinocyte stem cells, teaching that one may select a first population of cells from a partially enriched pool, and then provide a second enrichment step by separating cells with high and low binding levels from those which have low binding levels, using, for example antibodies and FACS techniques (col. 3, lines 49+-col. 4, lines 1-12, for example). Accordingly, Mahmud teach that pluripotent cells are slow-cycling, which would clearly maintain higher levels of reporter protein than cells that are dividing, and the '971 document provides clear guidance as to how to separate cells that have higher versus lower levels of protein expression.

Accordingly, the '618 document provides guidance with regard to isolation of lineage-specific cells, and both Strathdee and Bohl teach methods of inducible gene expression that can efficiently be switched on and off, and avoid the art-recognized problem of cellular toxicity. Additionally, Strathdee provide motivation for utilizing this type of system in specific cell types and Bohl provide guidance to show that using a cell-specific promoter, one can efficiently express a gene of interest in a cell type of interest. Mahmud and the '971 document provide sufficient guidance to show that one of skill in the art would be readily apprised that stem cells are considered slow-cycling, and the '971 document provides sufficient guidance to separate cells based on the amount of reporter gene expression.

Thus, it would be obvious to one of skill in the art, to modify the '618 document to utilize a vector system such as that taught by Strathdee or Bohl,

utilizing a regulatable transcription factor operably linked to a cell-specific (for example, a stem cell specific) promoter, and a nucleic acid sequence encoding a reporter protein operably linked to a regulated promoter in which the regulatable transcription binds, using, for example, the tetracycline responsive expression system taught by both Strathdee and Bohl, and utilizing a reporter protein, such as any of those suggested by the '618 document, in order to FACS sort a protein, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of the teachings of both Strathdee and Bohl, who suggest utilizing these techniques in lineage-specific cells, and teach that utilizing their systems overcome the art-recognized problem of cellular toxicity (see, for example, Strathdee at p. 22, 1st col., 1st full ¶). One of skill in the art would be further motivated, in view of the teachings of Mahmud and the '971 document, to inactivate the regulatable transcription factor (by, for example, the withdrawal of doxycycline in the case of using the Tet system), and select for slow-cycling stem cells by allowing the cells to divide, and selecting cells that contain a higher level of reporter protein expression. One of ordinary skill in the art would have been sufficiently motivated to make this modification in order to produce substantially pure populations of stem cells. Although the pieces of art cited do not all recite isolation of the same types of stem cells, the provide sufficient guidance to show that the art is replete in methods for isolation and purification of stem cells, using various techniques that would be readily available to the skilled artisan.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 8, 10-14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat. No. 5,639,618 (Filed May 13, 1994, Issued June 17, 1997, IDS) when taken with Strathdee *et al.* (**Gene**, 229: 21-29, 1999), Bohl *et al.*(**Nat. Med.**, 3(3):

229-305, 1997) when taken with Mahmud *et al.* (**Blood**, 97(10): 3061-3068, 2001) and US Pat. No. 6,485,971 (filed September 18, 2000, Issued November 26, 2002) as applied to claims 7 and 9 above, and further in view of US Pat No. 5,665,557 (Filed November, 1994; Issued September 9, 1997).

Applicants provide the same arguments as above, which have been addressed.

The '618 document, Strathdee, Bohl, Mahmud and the '971 document are discussed above. They do not specifically teach sorting the population of cells based on the presence of CD34 and the amount of a selected slow-cycling cell marker. However, prior to the time of the claimed invention, the '557 document teaches obtaining an enriched population of hematopoietic stem cells by obtaining a population of human hematopoietic cells, separation of hematopoietic cells from a source, separating a subpopulation of cells utilizing a CDw109 antibody, and then using an additional maker to separate the cells, such as CD34, Thy-1 and rho. The limitations of claims 11-14 are considered inherent properties of the cell that would be isolated.

Accordingly, it would have been obvious to modify the combined teachings of the '618 document, Strathdee, Bohl, Mahmud and the '971 document, as outlined above, to separate a population of cells based on the presence of CD34 and a selected slow-cycling cell marker, such as any taught by the '577 document, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification to produce a substantially pure population of hematopoietic stem cells.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 15-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Strathdee *et al.* (**Gene**, 229: 21-29, 1999), Bohl *et al.*(**Nat. Med.**, 3(3): 229-305,

1997) when taken with Mahmud *et al.* (**Blood**, 97(10): 3061-3068, 2001) and US Pat. No. 6,485,971 (filed September 18, 2000, Issued November 26, 2002) and US Pat No. 5,665,557 (Filed November, 1994; Issued September 9, 1997)as applied to claims 7-14 above, and further in view of US Pat. No. 5,861,315 (Filed October 16, 1996; Issued January 19, 1999).

Applicants provide the same arguments as above, which have been addressed.

Strathdee, Bohl, Mahmud, the '971 document, the '557 document are detailed above. The combined art does not specifically teach or suggest a clonal population that comprises the cells of claims 9 or 10. However, prior to the time of the claimed invention, the '315 document teaches the clonal culture of CD34+ hematopoietic stem cells (col. 6, lines 5+).

Accordingly, it would have been obvious to the skilled artisan to utilize the combined art of Strathdee, Bhol, Mahmud, the '971 document, the '557 document to produce sorted cells that are self-renewing, multipotent, slow-cycling cells (claim 7), and particularly cells that are sorted based on the presence of CD32 and the amount of a selected slow-cycling cell marker (claim 8), and to then produce a clonal population of these cells, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make a clonal population of cells, such as hematopoietic stem cells for the methylcellulose assay such as that detailed in the '315 patent to analyze the differentiation potential of the cells. Additionally, a clonal population would ensure uniformity in the cell population, which could then be used for other purposes, such as gene therapy.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632